

REMARKS/ARGUMENTS

Applicants have not dedicated or abandoned any unclaimed subject matter and have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Status of the Claims

Claims 1-47 and 62 are canceled. Claims 48-60 are withdrawn from consideration. As such, claims 61 and 63-73 are currently under consideration in this application.

Claim 61 is amended to clarify that the first conjugate comprises “a first marker molecule and a first protein”, which is supported throughout the specification, for example, in paragraphs [0055] through [0060] of the published application. Claim 61 is further amended to clarify that the first protein of the first conjugate is “associated with the desensitization pathway of said first GPCR”, which is supported, for example, in paragraphs [0058] through [0060]. These amendments are thus fully supported by the specification and add no new matter.

Claims 63-65 are amended to clarify that the first or second marker molecule may be one of the recited molecules. As such, these amendments add no new matter.

Claims 67-68 are amended to clarify the proteins of the conjugates recited in claim 61. As such, these amendments add no new matter.

Applicants respectfully request entry of the claims as amended.

Elections/restrictions

The Office Action states on page 2 that claims 48 to 72 are withdrawn from further consideration as being drawn to a non-elected invention. Applicants note that only claims 48-60 are withdrawn from consideration – claims 61 through 72 read on the elected invention, as is stated on the Office Action Summary (Form PTOL-326). Applicants presume that the statement on page 2 of the Office Action is a typographical error and should state claims 48 to 60 are withdrawn from consideration.

Drawings

The attached sheets of replacement drawings include changes to Figures 2 and 3 (total of 7 sheets). Figures 2 and 3 have been renumbered in compliance with 37 C.F.R. § 1.84(U)(1). No new matter is added by these changes, and Applicants respectfully request entry of the corrected drawings.

Specification

The Office Action states on page 3 that the specification requires a reference to a particular sequence identifier to be in compliance with 37 C.F.R. §1.821(d). The Office Action further states that the amino acid sequence “NPXXY” is referred to throughout the specification without employing a sequence identifier. Applicants respectfully submit that the amino acid sequence NPXXY does not require a sequence identifier. 37 CFR 1.821(a) states that “Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. The amino acid sequence “NPXXY” has fewer than four specifically defined amino acids, and thus a sequence identifier is not required.

The sequence identifier for “TTIST” on page 16 line 4 is included in the substitute specification submitted with this response. Applicants respectfully submit that all objections to the specification are now moot and may be withdrawn.

Rejections under 35 USC § 112

Claims 61 to 66 and 68 to 73 are rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the written description and enablement requirements. Applicants respectfully disagree.

The Office Action asserts that the only compound described in the instant specification or the art of record that is capable of functioning in the context of the instant invention is an arrestin protein. Applicants respectfully submit that several examples of proteins associated with the desensitization pathway are known in the art and described in the instant specification. For example, in paragraph [0042] of the published application, the “GPCR desensitization pathway” is described as including not only arrestin but also GRKs, GPCRs, AP-2 protein, clathrin, protein

phosphatases, as well as other molecules. In addition, conjugates of the invention are described in paragraphs [0107] through [0113] as including arrestins or GPCRs, including modified GPCRs.

As will be appreciated, an adequate written description of the invention "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." *MPEP* §2163. Applicants submit that the present specification provides sufficient identifying characteristics of the claimed invention to fulfill the written description requirement. Several different proteins that can function as a conjugate of the invention are described in sufficient detail to convey to one of skill in the art that the inventors were in possession of the invention at the time of filing. In addition, working examples of multiplex receptor assays utilizing exemplary conjugates are provided in the present specification. Together, the description and the examples of the present specification would convey to one of skill in the art that the inventors were at the time the present application was filed in possession of the claimed invention, and that this claimed invention includes conjugates comprising arrestin as well as other molecules, such as GPCRs and GRKs. As such, the present claims fully comply with the written description requirement of 35 USC. §112, first paragraph.

Furthermore, the test of enablement is whether one reasonably skilled in the art could make or use the invention as claimed from the disclosure in the patent coupled with information known in the art without undue experimentation. *United States v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). *See also* *MPEP* §2164.01. One way to determine if undue experimentation is required is to utilize the *Wands* factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." All of the factors need not be reviewed when determining whether a disclosure is enabling. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

Applicants submit that the description of the different molecules associated with the GPCR desensitization pathway (as described above) coupled with the working examples of multiplex receptor assays using exemplary conjugates of the invention provides sufficient guidance such that the present application complies with the enablement requirement of 35 USC §112, first paragraph. The amount of direction or guidance presented is sufficient to allow one of skill in the art to practice the claimed invention without undue experimentation. As discussed above, the characteristics of the types of molecules that can be included in conjugates of the invention, as well as specific examples of components of these conjugates, are described in detail throughout the present specification. Since the types of molecules associated with the desensitization pathway are described in the specification and known in the art, one of skill in the art would readily understand the scope of the invention in terms of what kinds of conjugates can be used in accordance with the invention. Furthermore, the present specification provides working examples of multiplex receptor assays in which different conjugates are described and used to analyze different test compounds. One of skill in the art would therefore have sufficient guidance as to the creation and use of conjugates of the claimed invention – see for example, paragraphs [0118] through [0125]. As will be appreciated, although not every possible conjugate encompassed by the present claims is described in the working examples, Applicants respectfully submit that such description is not a requirement for enablement. The specification need not contain multiple working examples if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.¹ Furthermore, “[n]othing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples.”² One of skill in the art could use the description of the present specification to make and use any conjugate encompassed by the claims without undue experimentation. As such, Applicants respectfully submit that the enablement requirement of 35 USC §112, first paragraph is fully met by the present specification and claims.

¹ *In re Borkowski*, 164 USPQ at 645.

² *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

For at least the foregoing reasons, Applicants respectfully request that the rejections under 35 USC §112, first paragraph be withdrawn.

Rejections under 35 USC § 102(b)

Claims 61 to 73 are rejected under 35 USC 102(b) as allegedly being anticipated by Barak et al., U.S. Patent No. 5,891,646 ("Barak"). Applicants respectfully disagree.

To maintain a *prima facie* case of anticipation, the Office Action must demonstrate that each and every element as set forth in the claim is either expressly found or is inherently described in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the ...claim. *See MPEP § 2131.*

Applicants respectfully submit that every element of the instantly claimed invention is not described in Barak. Barak fails to describe or suggest a method of screening in which a cell comprises two different GPCRs and two different marker conjugates. Although Barak does describe cells that express multiple GPCRs, Barak does not describe or suggest any kind of method that is able to show which of the multiple GPCRs is affected by the test composition. As such, Barak fails to describe the claimed methods which utilize cells that comprise the elements of a first and second GPCR, where the second GPCR is different from the first GPCR, and a first and second conjugate, where the first conjugate includes a protein associated with the desensitization pathway of the first GPCR and the second conjugate includes a protein associated with the desensitization pathway of the second GPCR. Nor does Barak describe the elements of detecting a first and a second conjugate. The methods in Barak, even with cells expressing multiple GPCRs, cannot provide data that distinguishes the effect of a test composition among the different GPCRs. As such, Barak cannot describe every element of the presently claimed invention.

For at least the foregoing reasons, Barak fails to fulfill the requirements for a finding of anticipation under 35 USC §102(b). As such, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

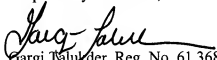
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

While Applicants believe that no other fees are due at this time, the Commissioner is authorized to charge any fees, including extension fees or any other relief that may be required, in connection with this reply to Deposit Account 50-0310 (Docket No.: 067437-5021-US)

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1266.

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Respectfully submitted,



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FIG. 2A

Human G Protein Coupled Receptor Family
(Receptors known as of January, 1999)

CLASS	LIGAND	NUMBER	TISSUE	PHYSIOLOGY	THERAPEUTICS
Class I Rhodopsin like					
	•Amine				
	•Acetylcholine (muscarinic & nicotinic)	5	Brain, Nerves, Heart	Neurotransmitter	Acuity, Alzheimer's
	•Adrenoceptors				
	•Alpha Adrenoceptors	6	Brain, Kidney, Lung	Glucoreogenesis	Diabetes, Cardiovascular
	•Beta Adrenoceptors	3	Kidney, Heart	Muscle Contraction	Cardiovascular, Respiratory
	•Dopamine	5	Brain, Kidney, GI	Neurotransmitter	Cardiovascular, Parkinson's
	•Histamine	2	Vascular, Heart, Brain	Vascular Permeability	Anti-inflammatory, Ulcers
	•Serotonin (5-HT)	16	Most Tissues	Neurotransmitter	Depression, Insomnia, Analgesic
	•Peptide				
	•Angiotensin	2	Vascular, Liver, Kidney	Vasoconstriction	Cardiovascular, Endocrine
	•Bradykinin	1	Liver, Blood	Vasodilation,	Anti-inflammatory, Asthma
	•C5a anaphylatoxin	1	Blood	Immune System	Anti-inflammatory
	•Ficol-leu-plie	3	Blood	Chemoattractant	Anti-inflammatory
	•Interleukin-8	1	Blood	Chemoattractant	Anti-inflammatory
	•Chemokine	6	Blood	Chemoattractant	Anti-inflammatory
	•Orexin	2	Brain	Fat Metabolism	Obesity
	•Nociceptin	1	Brain	Bronchodilator, Pain	Airway Diseases, Anesthetic
	•CCK (Gastrin)	2	Gastrointestinal	Motility, Fat Absorption	Gastrointestinal, Obesity, Parkinson's
	•Endothelin	2	Heart, Bronchus, Brain	Muscle Contraction	Cardiovascular, Respiratory
	•Melanocortin	5	Kidney, Brain	Metabolic Regulation	Anti-inflammatory, Analgesics
	•Neuropeptide Y	5	Nerves, Intestine, Blood	Neurotransmitter	Behavior, Memory, Cardiovascular
	•Neurotensin	1	Brain,	CNS	Cardiovascular, Analgesic
	•Opioid	3	Brain,	CNS	Depression, Analgesic
	•Somatostatin	5	Brain, Gastrointestinal	Neurotransmitter	Oncology, Alzheimer's

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FIG. 2B

•Tachykinin (Substance P, NK ₁)	3	Brain Nerves	Neurohormone	Depression, Analgesic
•Thrombin	3	Platelets, Blood Vessels	Coagulation	Anti-coagulant, Anti-inflammatory
•Vasopressin-like	4	Arteries, Heart, Bladder	Water Balance	Anti-diuretic, Diabetic Complications
•Galatin	1	Brain, Pancreas	Neurotransmitter	Analgesics, Alzheimer's
•Hormone protein				
•Follicle stimulating hormone	1	Ovary, Testis	Endocrine	Infertility
•Lutropin-choriogonadotropic	1	Ovary, Testis	Endocrine	Infertility
•Thyrotropin	1	Thyroid	Endocrine	Thyroidism, Metabolism
•(Rhodopsin				
•Opsin	5	Eye	Photoreception	
•Olfactory	4 (~1000)	Nose	Smell	Ophthalmic Diseases
•Prostanoid				Olfactory Diseases
•Prostaglandin	5	Arterial, Gastrointestinal	Vasodilation, Pain	Cardiovascular, Analgesic
•Lysophosphatidic Acid	2	Vessels, Heart, Lung	Inflammation	Cancer, Anti-Inflammatory
•Sphingosine-1-phosphate	2	Most Cells	Cell proliferation	Cancer
•Leukotriene	1	White Blood Cells,		
		Bronchus	Inflammation	Asthma, Rheumatoid Arthritis
•Prostacyclin	1	Arterial, Gastrointestinal	Platelet Regulation	Cardiovascular
•Thromboxane	1	Arterial, Bronchus	Vasoconstriction	Cardiovascular, Respiratory
•Nucleotide-like				
•Adenosine	4	Vascular, Bronchus	Multiple Effects	Cardiovascular, Respiratory
•Purinceptors	4	Vascular, Platelets	Relaxes Muscle	Cardiovascular, Respiratory
•Caenabis 2	Brain	Sensory Perception	Analgesics, Memory	Cardiovascular, Respiratory
•Platelet activating factor	1	Most Peripheral Tissues	Inflammation	Anti-inflammatory, Anti-asthmatic
•Gonadotropin-releasing hormone like				
•Gonadotropin-releasing hormone	1	Reproductive Organs,	Reproduction	Prostate Cancer, Endometriosis
		Pituitary		
•Thyrotropin-releasing hormone	1	Pituitary, Brain	Thyroid Regulation	Metabolic Regulation
•Growth hormone-inhibiting factor	1	Gastrointestinal	Neuroendocrine	Oncology, Alzheimer's
•Melatonin	1	Brain, Eye, Pituitary	Neuroendocrine	Regulation of Circadian Cycle

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FIG 3A

G protein-coupled receptors:

(Division into Class A

Or Class B)

1. **A1 adenosine receptor** [Homo sapiens]. ACCESSION AAB25533
NPITYAF RIQKFRVTFL KIWNDFRCQ PAPIDEDLP EERPDD
Class A (SEQ ID NO: 1)
2. **adrenergic, alpha -1B-, receptor** [Homo sapiens]. ACCESSION NP_000670
npitypc skkefkrafv rilgeqcrgr gmmmmr lggcaytyrp wrtgsglers qrikdsldds gscsgsqrq lpsaspspgy
lgrgappvpe lcafpewkap gallsipape ppgtrgrids gplftklit epespqtdgg asnggceaaa dvangpqpqk
smmplapqgf
Class A (SEQ ID NO: 2)
3. **adrenergic receptor alpha-2A** [Homo sapiens]. ACCESSION AAG00447
npviyifn hdftrafkci lorgdrkriv
Class A (SEQ ID NO: 3)
4. **alpha-2B-adrenergic receptor - human**. ACCESSION A37223
npviyifn qdftrafri lerpwtqaw
Class A (SEQ ID NO: 4)
5. **alpha-2C-adrenergic receptor - human**. ACCESSION A31237
npviyifn qdftrafkci lfmrrgr q
Class A (SEQ ID NO: 5)
6. **beta-1-adrenergic receptor** [Homo sapiens]. ACCESSION NP_000675
npitycsp pdfrikaqgl locarraar rhatgdrpr asgclarpgp ppspgaaadd ddddvvgatp parllepwag
cnggaasdsd ssldpcprg fassskv
Class A (SEQ ID NO: 6)
7. **beta-2 adrenergic receptor**. ACCESSION P07550
npitycsp dfriaqell clrraskay gnyysangnt 361 geqsgyhveq ekenkloed lpgtdfvgh qgtvpsdnid
sqgncstnd sll
Class A (SEQ ID NO: 7)
8. **dopamine receptor D1** [Homo sapiens]. ACCESSION NP_000785
npii yaftadrika fstllgcyl cpatmaiet vsinnngaam fssheprgs iskecnlvyl iphavgsed lkkeeaagia
rpleklspal svldydtvd slekiqpitq ngqhtp
Class A (SEQ ID NO: 8)
9. **D(2) dopamine receptor**. ACCESSION P14416
npiiytfn iefikaflki the
Class A (SEQ ID NO: 9)

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FIG 3B

10. **d3 dopamine receptor - human. ACCESSION G01977**
np viytfniief rkafikilsc
Class A (SEQ ID NO: 10)
11. **dopamine receptor D4 - human. ACCESSION DYHUD4**
npviyiv fnacfnvfr kalracc
Class A (SEQ ID NO: 11)
12. **dopamine receptor D5 - human. ACCESSION DYHUD5**
npviya fnadfqkvfa qllgshfcs rtpvetvnis nelisyngdi vfhkciaaay ihmmpnavtp gnrevdndee
egpfdrmfqi yqtspdgdpv acswelddce geisldkctip fipngfh
Class A (SEQ ID NO: 12)
13. **muscarinic acetylcholine receptor M1 [Homo sapiens]. ACCESSION NP_000729**
nprncyal cnkafidtr llllcrwdkr rwrkclprg svhrtpsrqc
Class A (SEQ ID NO: 13)
14. **muscarinic acetylcholine receptor M2 [Homo sapiens]. ACCESSION NP_000730**
npacy alcnatfkkt fikhllmchyk nigatr
Class A (SEQ ID NO: 14)
15. **muscarinic acetylcholine receptor M3 [Homo sapiens]. ACCESSION NP_000731**
n pveyalcnkt fttfkmlll cqqdkkkrrk qyyqqrsvi fhkrapeql
Class A (SEQ ID NO: 15)
16. **muscarinic acetylcholine receptor M4 [Homo sapiens]. ACCESSION NP_000732**
npa cyalcnatfk ktfrhllc qymigtar
Class A (SEQ ID NO: 16)
17. **m5 muscarinic receptor. locus HUMACHRM ACCESSION AAA51569**
npicyalcnr tfrtkfcmll lcrwkdkkve ckywagnsk lp
Class A (SEQ ID NO: 17)
18. **5-hydroxytryptamine (serotonin) receptor 1A [Homo sapiens]. ACCESSION BAA90449**
npviy ayfukdfqna fckikokcf
Class A (SEQ ID NO: 18)
19. **5-hydroxytryptamine (serotonin) receptor 1B [Homo sapiens]. ACCESSION BAA94455**
npiiyt msnedkfqaif hckirfkots
Class A (SEQ ID NO: 19)
20. **5-hydroxytryptamine (serotonin) receptor 1E [Homo sapiens]. ACCESSION BAA94458**
n pllytsfnd fclafdkdir cre
Class A (SEQ ID NO: 20)

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FIG 3C

21. **OLFACTORY RECEPTOR 6A1. ACCESSION O95222**
 npiiyclrnq evkralcoil hlyqhqdpdp kkgsmnv
 Class A (SEQ ID NO: 21)

22. **OLFACTORY RECEPTOR 2C1. ACCESSION O95371**
 nplyi tirmmekga lrrllgkgrc vg
 Class A (SEQ ID NO: 22)

23. **angiotensin receptor 1 [Homo sapiens]. ACCESSION NP_033611**
 npl fygfigkckfk ryflqllkyi ppkakshsnl stkmstfsyr psdnvssstk kpacpfvev
 Class B (SEQ ID NO: 23)

24. **angiotensin receptor 2 [Homo sapiens]. ACCESSION NP_000677**
 npflycf vgnrfqqkkr svfrvptwl qgkresmscr kssslremet fvs
 Class B (SEQ ID NO: 24)

25. **interleukin 8 receptor beta (CXCR2) [Homo sapiens]. ACCESSION NM_001557**
 NPLIYAFIGQKFRHGLLKILAIHGLISKDSLPKDSRPSFVGSSSGHTSTTL
 Class B (SEQ ID NO: 25)

26. **cx3c chemokine receptor 1 (cx3cr1) (fractalkine receptor)**
 ACCESSION P49238
 np liyafagckf rrylyhlygk clavicgrsv hvdffsscsq rwrhgsvlss nftyhtsdgd allll
 Class B (SEQ ID NO: 26)

27. **neurotensin receptor - human. ACCESSION S29506**
 n piylnlvsan fhiflatla olcpvwmrrr krpfafskad svssnhfss natretly
 Class B (SEQ ID NO: 27)

28. **SUBSTANCE-P RECEPTOR (SPR) (NK-1 RECEPTOR) (NK-1R). ACCESSION P25103**
 npiiyccldn rfrlglkhafr rccpfisagd yeglemkstr yltqtgsvyk vsrletfstvvgahcepe dgpkatpss!
 dltncssrs dsktmtesfs fsnvlv
 Class B (SEQ ID NO: 28)

29. **vasopressin receptor type 2 [Homo sapiens]. ACCESSION AAD16444**
 npwiyasfss svssclrall ccargtpps lgpqdescff asslakdts s
 Class B (SEQ ID NO: 29)

30. **thyrotropin-releasing hormone receptor - human. ACCESSION JN0708**
 npviy nimsqkfnaa fklcnckqk ptekpnyysv alnysvikes dhfstelddi tvtdtylsaf kvsfddtola sevsfaqs
 Class B (SEQ ID NO: 30)

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FIG 3D

31. **oxytocin receptor - human**. ACCESSION A55493
 npwiyw lftghlfhel vqrflccsas ylkgrtget saskckmass fvlsrsshq rscsqpsta
 Class B (SEQ ID NO: 31)

32. **neuromedin U receptor [Homo sapiens]**. ACCESSION AAG24793
 npvlyslmsrfrtfealclgacchrlprhshslsmtgtstlcdvsglswvhlplagndgpeaqcetdps
 Class B (SEQ ID NO: 32)

33. **gastrin receptor**. ACCESSION AAC37528
 nplyv ofnhrrfqa cletcarcep rprarpral pdcppptpsi aslsrlsytt tsflgpg
 Class B (SEQ ID NO: 33)

34. **galanin receptor 3 [Homo sapiens]**. ACCESSION I0879541
 nplv yalasrhfra rfrirwpcgr rrrharal rrvpassgp pgcpgdarps grillaggggg pepregpvhg geaargpe
 Class A (SEQ ID NO: 34)

35. **edg-1 - human**. ACCESSION A35300
 npiiy tlnkemrra firimsocck psqdsagkfk rpiagmefi rsk&dnshp 361 qkdegdnpet imssgnvns s
 Class A (SEQ ID NO: 35)

36. **central cannabinoid receptor [Homo sapiens]**. ACCESSION NP_057167
 npiiyalr skdlrhafis mfpsoegtaq pldnsmgdsd clkhannaa svhraacsci kstvkiaqvt msvstdtsac al
 Class A (SEQ ID NO: 36)

37. **delta opioid receptor - human**. ACCESSION I38532
 npvlyaf ldenkrcfr qlckpcgrp dpssfspre atarvtac tpsdpggggr aa
 Class A (SEQ ID NO: 37)

38. **proteinase activated receptor 2 (PAR-2) human**. ACCESSION P55085
 dpfvyyfvsbdfdrhaknallcrrsvrtvkqmqsitskhhsksssyssstivktsy
 Class A (SEQ ID NO: 38)

39. **vasopressive intestinal peptide receptor (VIPR) rat**. ACCESSION NM_012685
 NGEVQAELRRKWRRWHLQGVLGWSSKSQHPWGGSGNGATCSTQVSMLTRVSPSARR
 SSSFQAEVSLV
 Class B (SEQ ID NO: 39)